

Quality of life in multiple sclerosis (MS) and role of fatigue, depression, anxiety, and stress: A bicenter study from north of Iran

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ABSTRACT

Background: Although studies have demonstrated significant negative relationships between quality of life (QOL), fatigue, and the most common psychological symptoms (depression, anxiety, stress), the main ambiguity of previous studies on QOL is in the relative importance of these predictors. Also, there is lack of adequate knowledge about the actual contribution of each of them in the prediction of QOL dimensions. Thus, the main objective of this study is to assess the role of fatigue, depression, anxiety, and stress in relation to QOL of multiple sclerosis (MS) patients.

Materials and Methods: One hundred and sixty-two MS patients completed the questionnaire on demographic variables, and then they were evaluated by the Persian versions of Short-Form Health Survey Questionnaire (SF-36), Fatigue Survey Scale (FSS), and Depression, Anxiety, Stress Scale-21 (DASS-21). Data were analyzed by Pearson correlation coefficient and hierarchical regression.

Results: Correlation analysis showed a significant relationship between QOL elements in SF-36 (physical component summary and mental component summary) and depression, fatigue, stress, and anxiety ($P < 0.01$). Hierarchical regression analysis indicated that among the predictor variables in the final step, fatigue, depression, and anxiety were identified as the physical component summary predictor variables. Anxiety was found to be the most powerful predictor variable amongst all ($\beta = -0.46$, $P < 0.001$). Furthermore, results have shown depression as the only significant mental component summary predictor variable ($\beta = -0.39$, $P < 0.001$).

Conclusions: This study has highlighted the role of anxiety, fatigue, and depression in physical dimensions and the role of depression in psychological dimensions of the lives of MS patients. In addition, the findings of this study indirectly suggest that psychological interventions for reducing fatigue, depression, and anxiety can lead to improved QOL of MS patients.

Key words: Anxiety, depression, fatigue, multiple sclerosis, quality of life, stress

INTRODUCTION

According to the definition of World Health Organization (WHO), quality of life (QOL) is “the individual’s perception of his/her position in life in the context of the culture, value systems in which he/she lives, and in relation to his/her goals, expectations, standards and concerns”.^[1]

Studies have identically shown that patients with multiple sclerosis (MS) experience lower QOL compared to healthy

control group.^[2,3] Fatigue is the most common symptom of MS.^[4] In addition to the chronic nature of the disease, lack of prognosis and a definitive therapy besides suffering from it from early adulthood causes several psychological symptoms among which depression, anxiety, and stress are the most common.^[5] In recent years, there has been an increase in the number of studies on the relationship between these factors and QOL in MS.^[2,3,6-17] Overall, these studies have demonstrated significant relationship between fatigue and psychological symptoms with QOL dimensions. In these studies, low QOL has been predicted by fatigue^[8,9,10,12] and psychological symptoms, especially depression and anxiety.^[2,3,6,8-12,14] There is skepticism about the relative importance of these predictors, especially fatigue and depression, as with regard to QOL of MS patients, some researches in which fatigue and depression were studied simultaneously have proved fatigue^[12] to be the more powerful predictor and some others have proved depression^[10] to be the stronger variable, while anxiety has been relevant only in some

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Submitted: 12-May-13; Accepted: 29-Mar-14

QOL studies^[6,11] and in others it has not emerged as a significant predictor of QOL.^[7] Moreover, there is a shortcoming in the studies of stress in relation to QOL of MS patients. For example, researchers have focused more on the effects of stress on exacerbations and relapses,^[18-20] new brain magnetic resonance imaging (MRI) lesions,^[21] inflammation,^[22] radiological disease activity,^[23] and depressive symptoms^[24] of MS patients and mainly are marginalized the role of stress in reducing the physical and psychological aspects of patients QOL. But in a cross-sectional investigation, we have demonstrated that QOL has a negative correlation with all three symptoms of depression, anxiety, and stress (sequenced based on the degree of significance).^[17]

Thus, the major weakness of previous studies is the existence of inconsistency in the findings about the contribution of each of the symptoms of fatigue, depression, anxiety, and stress in predicting the physical and psychological aspects of QOL of MS patients. Furthermore, some of the studies on QOL of MS patients have not attempted to control the confounding factors or have chosen very small sample size of patients.^[25] Hence, the present study aims to evaluate the role of each of the mentioned symptoms in predicting the QOL of people with MS.

MATERIALS AND METHODS

Ethical considerations

Conducting the research was approved by the appropriate research committee of University of Guilan. Verbal information about the research study was provided for patients and written informed consent was given by patients. Patients also informed about their right to withdraw from the study at any time if they so desired.

Participants

This study was conducted in 2010 by descriptive cross-sectional method in patients with MS supported by the MS Society of Guilan Province (north of Iran). One hundred and sixty-two patients were selected by consecutive sampling as the study sample. Inclusion criteria included patients diagnosed with MS disease based on McDonald criteria,^[26] with the diagnosis confirmed by a neurologist. The existence of MS disease was determined by the symptoms and clinical characteristics of the patient and also by the clinical evidence of lesion in two or more regions of the central nervous system (CNS). In order to confirm the damage, paraclinical measures such as MRI, evoked potential (EP), and cerebrospinal fluid (CSF) levels were used and patients who had a record at MS Society were confirmed of the diagnosis of the disease based on the mentioned findings. The exclusion criteria were: (a) occurrence of severe MS attack, (b) presence of severe cognitive problems due to

which the patient was not able to fill in the tools and answer the interviewer, and (c) existence of any debilitating disease or physical issue associated with MS.

Procedure

This research was conducted in the MS Society of Guilan Province and Imam Reza Specialized and Sub-specialized Clinic. At the beginning of sampling, patients who satisfied the inclusion criteria were contacted and referred to the clinic. During the initial assessment, an explanation about the objectives of the study and the methods of research had been given to the patient and his/her family or companion. Also, patients were assured of the confidentiality of the measurements. Finally, after the patient and his/her family or companion signed the consent form, the patient entered the study. Data collection was with the help of a questionnaire and scale which included a section for demographic information and other sections for QOL assessment, fatigue severity, and psychological symptoms of MS patient. Subjects were asked to first fill up the demographic information list and then fill up the questionnaire and scale under the supervision of a psychologist who was present at the study location.

Measurement tools

Demographic variables list for MS patients

In this study, based on the demographic characteristics of patients, data related to age, sex, marital status, education level, personal and family background of visiting a psychologist or a psychiatrist, and duration of MS (in months) were collected.

Short-form health survey questionnaire

This questionnaire was prepared by Ware *et al.*^[27] It includes 36 questions and provides two general measures of function: Physical component summary (PCS) and mental component summary (MCS).^[28] Each question is scored from 1 to 100 and scores close to 100 indicate better QOL. In this regard, a study was conducted to confirm the validity and reliability of the Persian translation of Short-Form Health Survey Questionnaire (SF-36).^[29] In general, the findings showed that Persian translation of SF-36 is an appropriate measuring tool for assessing health perceptions.

Fatigue severity scale

The Persian version of this tool had been used to measure the fatigue severity. This tool, which was initially created by Krupp to measure the fatigue level of MS patients, is a nine-item scale that examines the amount of fatigue with scores ranging from 1 to 7. The criterion validity of this tool has been reported as 0.68 and the internal consistency coefficient as 0.81.^[30] By examining different aspects of the Persian version of Fatigue Severity Scale (FSS), it has been proved that the Persian version is an appropriate psychometric tool for assessing MS patients.^[31]

Depression, anxiety, stress scale-21

Persian version of this instrument which was originally presented by Lovibond and Lovibond^[32] has been used to assess depression, anxiety, and stress of patients. Espinola-Nadurille et al. have also recommended the use of tools that measure several symptoms in the cases of neurological disorders with psycho-neuro symptoms.^[33] This scale has 21 questions and each of three sub-scales includes seven questions, the scores of which are obtained by summing up the scores of related questions. Evidences confirm the preliminary reliability and preliminary construct validity of the Persian translation of Depression, Anxiety, Stress Scale-21 (DASS-21).^[34]

Statistical analyses

To describe the data in this study, descriptive statistical indicators like percentiles, mean, and standard deviation were used. In the inferential statistics section, we applied Pearson correlation analysis to test the relation hypotheses. Also, hierarchical regression was used in order to measure the influence of fatigue, depression, anxiety, and stress on PCS and MCS components. Finally, based on the results of this statistical analysis which included non-standardized coefficient (B), standard deviation coefficient (SEB), Beta coefficients (β), R square (R^2), and F values, prediction models of PCS and MCS were derived for the psychological symptoms and fatigue.

RESULTS

Based on the inclusion and exclusion criteria, 162 patients of age between 16 and 58 years and with a mean age of 34.07 ± 9.44 years were included in this study. Of these, 29.6% were males and 70.4% were females (MS is more common in women). Marital status indicated that 21% were single, 75.9% married, 0.6% widowed, and 2.5% were divorcees. Moreover, 7.4% of patients had primary school education and 14.7%, 49.7%, and 28.2% had pre-high school, high school, and university education, respectively. Furthermore, findings show that 17.3% of MS patients had records of psychologist or psychiatrist appointments and 10.5% of MS patients

stated that one of their family members had visited experts. Finally, average duration of disease in these patients was 56.94 ± 56.08 months.

In order to test the hypothesis of supposed relations between PCS, MCS, fatigue, depression, anxiety, and stress, Pearson correlation method was applied. Table 1 indicates the mean, standard deviation, and intercorrelation between variables of the study. As can be seen, there was a high intercorrelation between the variables included in the study ($P < 0.01$).

Hierarchical regression analysis

Hierarchical regression analysis was applied to assess the effects of entered variables on PCS and MCS [Tables 2 and 3].

It can be seen in Table 2 that the total variance of all entered variables was 0.53 (R^2) in the third step ($P < 0.001$, $F = 15.95$). Yet, it has to be considered that additional variance in the final step, after controlling demographic variables such as age, sex, marital status, education level, personal and family background of visiting a psychologist or a psychiatrist, and duration of MS (in months), was estimated to be 0.33. It means that the main variables of the study have explained 33% of PCS variance, although it has to be noted that among the predictor variables, in the final step, only stress had not emerged as a significant variable ($\beta = 0.07$), whereas anxiety was the largest predictor variable at this stage ($\beta = -0.46$, $P < 0.001$) [Table 2].

Table 3 indicates that by considering all included variables, the total variance for MCS of third step was 0.51 (R^2) ($F = 15.26$, $P < 0.001$), although additional variance at this step and after controlling demographic variables was 0.38. Also, it has to be noted that among the predictor variables of the study and after controlling demographic factors, only depression stood as the significant predictor for MCS. This shows that depression alone has explained 38% of MCS variance ($\beta = -0.39$, $P < 0.001$) [Table 3].

Table 1: Mean, standard deviation, and intercorrelation between variables (N=162)

Variable	M (SD)	Correlation coefficients					
		1	2	3	4	5	6
PCS	26.28 (12.66)	1					
MCS	26.72 (11.87)	0.661**	1				
Fatigue	4.87 (1.70)	-0.432**	-0.343**	1			
Depression	8.33 (6.31)	-0.607**	-0.711**	0.367**	1		
Anxiety	7.64 (5.37)	-0.644**	-0.658**	0.309**	0.770**	1	
Stress	11.46 (5.78)	-0.546**	-0.700**	0.282**	0.820**	0.770**	1

PCS: Physical component summary, MCS: Mental component summary, SD: Standard deviation. ** $P < 0.01$

Table 2: Results of hierarchical regression to assess the effects of included variables on PCS

Variable entered	Statistical indices				
	B	SEB	β	R ²	F
Step 1					
Age	2.65	1.59	0.12		
Sex	-0.22	2.12	-0.01	0.20	11.25***
Marital status	-0.26	0.09	-0.26**		
Education level	0.28	0.07	0.28***		
Step 2					
Age	2.77	1.62	0.13		
Sex	-0.26	2.14	-0.01		
Marital status	-0.24	0.10	-0.24*		
Education level	0.31	0.08	0.31***	0.20	6.62***
Personal history	1.55	2.04	0.06		
Family history	1.58	2.47	0.05		
Duration	-0.04	0.08	-0.04		
Step 3					
Age	2.36	1.26	0.11		
Sex	1.73	1.66	0.07		
Marital status	-0.23	0.08	-0.23**		
Education level	0.01	0.07	0.01		
Personal history	-1.40	1.61	-0.05		
Family history	0.66	1.90	0.02	0.53	15.95***
Duration	0.02	0.06	0.02		
Fatigue	-0.18	0.06	-0.18**		
Depression	-0.22	0.10	-0.22*		
Anxiety	-0.46	0.09	-0.46***		
Stress	0.07	0.11	0.07		

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

DISCUSSION

The main objective of the present study was to find the role of psychological factors of depression, anxiety, and stress, and also fatigue in PCS and MCS components (in SF-36) of MS patients. Previous research evidences show that fatigue and psychological symptoms associated with MS are related to decrease in QOL of these patients.^[2,6,8-10,12,14,17] The findings of these researches are in accordance with the results of this study, as there was a significant relationship between physical and mental aspects of QOL with the factors of fatigue and psychological symptoms [Table 1]. The main interpretation of this finding is that fatigue can strongly influence performing the daily activities and become a major reason for unemployment,^[35] as the findings of McCabew and De Judicibus^[36] indicated that the pressures lead to changes in the economic situation and dealing with these pressures is momentous for QOL of MS patients. Furthermore, psychological symptoms can affect the self-efficiency and self-worthiness perception of

the MS patient because these symptoms can undermine the coping resources of the person. This issue can lead to deterioration in QOL of patients.

Moreover, results show that fatigue, depression, and anxiety are the major predictors of PCS for MS patients, while stress has not turned out to be a significant predictor [Table 2]. Our data conform with the previous reports.^[13,37] Also, findings of this study have been verified by Tafflefer *et al.*^[28] A recent study conducted on two groups of patients suffering from chronic fatigue syndrome (CFS) and MS indicated that in both groups, worse PCS in SF-36 was significantly associated with higher fatigue severity, though for none of these groups, MCS was not associated with fatigue severity. Results of this study also revealed that fatigue can only predict PCS and not MCS [Tables 2 and 3]. In accordance with our findings, Papuc and Stelmasiak found that fatigue and depression are the most powerful predictors for QOL of MS patients.^[3] A basic explanation for fatigue can be the link between physical damages and fatigue, especially its physical aspects, since because of damage to different regions of brain, thinking and activities demand higher energy than before. On the other hand, muscles with spasticity work against each other; therefore, more force is needed to perform physical activities. It has to be considered that fatigue is caused by cellular MS and is the result of disease process. Demyelination makes it harder for neurons to send signals.^[38] In fact, the increase in neuronal activity in cellular tissues, which occurs to compensate the problems, gradually leads to weakness of physical abilities and subsequently results in depletion of PCS in MS patients. Besides, one of the outcomes of depression is the feeling of lack of energy and illness that prevents the patient to endure physical pressures. Moreover, depression is probably associated with focal demyelinating lesions and malfunction of immune system.^[39] These complications can lead to functional limitations and generalized disorder in the PCS of patients.

Yet, in this study, anxiety has been identified as the strongest significant predictor for PCS. In an earlier study, Chylova *et al.*^[40] assessed the psychological situation of two groups of MS patients (using SF-36) and stated that anxiety was associated with the physical health situation of younger patients of MS. Although the findings of our study contradict the results of some studies,^[7] the differences can be attributed to the tools used in studies. In the latter study, Zung Anxiety Rating Scale (ZARS) was used as a separate tool to measure anxiety,^[7] whereas in this investigation, DASS, which assesses the psychological pathology of depression, anxiety, and stress, has been used. This could have affected the quality of findings, although it has to be noted that recent publications of MS have emphasized on the use of multi-symptom measuring tools.^[33] Yet, the anxiety of MS patients can be explained by natural etiology theory

Table 3: Results of hierarchical regression to assess the effects of included variables on MCS

Variable entered	Statistical indices				
	B	SEB	B	R ²	F
Step 1					
Age	0.14	0.17	0.06		
Sex	-0.40	0.22	-0.16	0.11	5.90***
Marital status	-0.004	0.01	-0.04		
Education level	0.02	0.01	0.25**		
Step 2					
Age	0.19	0.17	0.09		
Sex	-0.39	0.22	-0.16		
Marital status	-0.002	0.01	-0.02		
Education level	0.03	0.01	0.28***	0.13	4.31***
Personal history	0.53	0.21	0.20***		
Family history	-0.25	0.26	-0.08		
Duration	-0.002	0.01	-0.02		
Step 3					
Age	0.14	0.13	0.06		
Sex	-0.16	0.17	-0.07		
Marital status	-0.003	0.01	-0.03		
Education level	-0.005	0.01	-0.05		
Personal history	0.18	0.16	0.07		
Family history	-0.32	0.19	-0.10	0.51	15.26***
Duration	0.004	0.01	0.04		
Fatigue	-0.01	0.01	-0.06		
Depression	-0.04	0.01	-0.39***		
Anxiety	-0.02	0.01	-0.16		
Stress	-0.02	0.01	-0.21		

P<0.01; *P<0.001

or by bio-behavioral approaches that consider anxiety as an endogenous product which is created to confront hazardous stimuli and is naturally produced in situations wherein self is endangered - a mechanism that leads to drop in physiological functions and, therefore, decrease in indicators associated with QOL in patients. Also in this study, stress has not been identified as a significant variable for PCS. To explain this finding, it could be said that stress plays a common role in most of the personal and social behaviors of MS patients. Therefore, patients describe stress as "routine symptom", so that whenever encountered a question from the stress sub-category in DASS, such as "I tended to over-react to situations", they answered it as an usual experience or with low intensity. It must be noted that personal interpretations of the symptoms by patients play a critical role in their answers and ultimately their level of stress reported.

Our data showed that only depression is a significant predictor for MCS [Table 3]. This finding agrees with the previous reports on MS patients.^[10,15] One of these studies showed

depression as the most statistically significant predicting characteristic for MCS in SF-36.^[10] Moreover, Füvesi *et al.* also found that depressed MS patients had their QOL become worse in a significant way.^[41] Based on an interpretation of this finding, depression impairs motivation, interest, and collaboration of the patient; this consequently can affect vitality, social function, mental health, and generally MCS. Another interpretation is that depression can distort the viewpoints of people on the world and their health, and change it in a way that deteriorates their evaluation of self.^[42]

Overall, the findings revealed the role of anxiety, fatigue, and depression in physical aspects and the role of depression in mental aspects of lives of MS patients. Clinical application of this finding is to suggest rehabilitation interventions that reduce fatigue and destructive mental symptoms and consequently improve the qualitative aspects of life. In this regard, QOL-based psychotherapy, a non-drug, non-attack, and economical therapy toward promotion of physical and mental dimensions of life, can be utilized. By these psychotherapies, we can target the anxiety and fear of progress of the disease in patients and improve their knowledge of the nature of MS and ways to manage it. Moreover, cognitive restructuring programs, training programs for accommodating with physical damages, and cognitive behavioral therapy can be conducted. Note that in these kinds of psychotherapies, MS patients should be encouraged to do more exercises and active pleasurable physical activities. It should be noted that (a) fatigue is described as a multi-dimensional construct with symptoms such as decline in activity, decrease in energy, and slowness of organs and (b) greater extent of functional limitations predicts negative psychological symptoms overtime. It has been previously revealed that exercise program^[43] and aerobics^[44] can decrease fatigue and depression, improve positive thinking, and enhance participation in social acts, and ultimately have a positive effect on QOL of patients. It is necessary to remember that MS is a progressive and changing disorder, so patients suffering from it experience numerous transforming symptoms. Thus, perceiving QOL in MS is complex.

Samples of this study were not homogenous in terms of level of care, disease severity, amount of hospital measures, quality of care after affliction (especially in family environment), and social support style. Further, in this study, we did not consider the role of drugs that the patients were taking. This issue can play a role in the appearance of symptoms assessed in this research. Also, the presented data are self-reported and this can increase the possibility of biased and tampered answers in several tools. Another limitation of our study is the small size which can affect the results. Thus, the findings of this study should be generalized with caution.

Our data stressed the importance of the factors of fatigue and psychological symptoms in physical and mental aspects

of lives of MS patients. Therefore, our study suggests that future researches assess the treatment of fatigue and its psychological symptoms and its effect on QOL. Also, studies should aim more clearly at the possible contributing mechanisms in decreasing QOL of MS patients, such as immunomodulatory drugs, organic brain lesions due to disease, employment, and levels of coping. Finally, we suggest the use of experimental or longitudinal plans which provide the induction of causal relations between QOL and clinical and psychological factors in future researches.

CONCLUSION

This study revealed that PCS and MCS have significant negative relationships with any of the symptoms of fatigue, depression, anxiety, and stress. The results of the statistical analysis, after controlling for demographic and clinical variables, showed that fatigue, depression, and anxiety were the variables that significantly predicted PCS while anxiety appeared to have the strongest significance as a predictor. However, for MCS, only depression was identified as a significant variable. These results further highlight the impact of fatigue and psychological symptoms on QOL dimensions of patients with MS. Thus, based on the findings, management of patients' psychological and clinical symptoms to improve their QOL through programs such as psychotherapy interventions, exercise, and aerobics is recommended.

ACKNOWLEDGMENT

The authors of this paper would like to thank all MS patients who participated in this study despite having many disease-related problems.

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How to cite: Salehpoor G, Rezaei S, Hosseininezhad M. Quality of life in multiple sclerosis (MS) and role of fatigue, depression, anxiety, and stress: A bicenter study from north of Iran. *Iranian Journal of Nursing and Midwifery Research* 2014;19:593-9.

Source of Support: This research has been carried out without the support of any institution/organization, **Conflict of Interest:** Nil.